Exhibit 70

JAMA | Special Communication

Causal Inference About the Effects of Interventions From Observational Studies in Medical Journals

Issa J. Dahabreh, MD, ScD; Kirsten Bibbins-Domingo, PhD, MD, MAS

IMPORTANCE Many medical journals, including *JAMA*, restrict the use of causal language to the reporting of randomized clinical trials. Although well-conducted randomized clinical trials remain the preferred approach for answering causal questions, methods for observational studies have advanced such that causal interpretations of the results of well-conducted observational studies may be possible when strong assumptions hold. Furthermore, observational studies may be the only practical source of information for answering some questions about the causal effects of medical or policy interventions, can support the study of interventions in populations and settings that reflect practice, and can help identify interventions for further experimental investigation. Identifying opportunities for the appropriate use of causal language when describing observational studies is important for communication in medical journals.

OBSERVATIONS A structured approach to whether and how causal language may be used when describing observational studies would enhance the communication of research goals, support the assessment of assumptions and design and analytic choices, and allow for more clear and accurate interpretation of results. Building on the extensive literature on causal inference across diverse disciplines, we suggest a framework for observational studies that aim to provide evidence about the causal effects of interventions based on 6 core questions: what is the causal question; what quantity would, if known, answer the causal question; what is the study design; what causal assumptions are being made; how can the observed data be used to answer the causal question in principle and in practice; and is a causal interpretation of the analyses tenable?

CONCLUSIONS AND RELEVANCE Adoption of the proposed framework to identify when causal interpretation is appropriate in observational studies promises to facilitate better communication between authors, reviewers, editors, and readers. Practical implementation will require cooperation between editors, authors, and reviewers to operationalize the framework and evaluate its effect on the reporting of empirical research.

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Author Affiliations: CAUSALab, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Dahabreh); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Dahabreh); Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Dahabreh); Smith Center for Outcomes Research in Cardiology, Beth Israel Deaconess Medical Center, Boston, Massachusetts (Dahabreh); Statistical Editor, *JAMA* (Dahabreh); Department of Medicine, University of California, San Francisco (Bibbins-Domingo); Department of Epidemiology and Biostatistics, University of California, San Francisco (Bibbins-Domingo); Editor in Chief, *JAMA* and JAMA Network (Bibbins-Domingo).

Corresponding Author: Issa J. Dahabreh, MD, ScD, CAUSALab, Department of Epidemiology, Harvard T.H. Chan School of Public Health, 677 Huntington Ave, Room 816c, Boston, MA 02115 (idahabreh@hsph.harvard.edu).

Many medical journals, including *JAMA*, restrict the use of causal language to describing studies in which the intervention is randomly assigned. Indeed, randomized clinical trials are widely viewed as the preferred way of answering questions about the causal effects of interventions. Yet it is not feasible to answer all such questions with trials due to limitations including cost, follow-up duration, or ethical considerations. When such limitations preclude the conduct of trials, carefully designed analyses of observational (nonexperimental) data offer an alternative source of evidence on the effects of interventions (eg, treatment strategies, policies, or changes in behavior). Furthermore, observational studies can serve as a data-driven approach for identifying interventions that merit further experimental investigation and for examining the effects of interventions in populations and settings that reflect practice.

The potential of observational studies to contribute evidence about the causal effects of interventions is actively being examined across medicine, epidemiology, biostatistics, economics, and other social sciences. In this Special Communication, we examine a framework that might be used by medical journals as they move away from the current approach prohibiting the use of any causal language for observational studies and toward a more comprehensive approach for causal inference that reflects a synthesis of extensive prior work spanning multiple, diverse disciplines. We undertake this examination now for 3 main reasons. First, decision-makers are increasingly seeking timely answers to complex research questions about the effects of interventions that are challenging or impossible to address with randomized trials. For example, questions about long-term or rare effects of treatment, heterogeneity of treatment effects, or the effects of health care policies can be difficult to answer by relying exclusively on trials. Second, there has been wide dissemination of frameworks for posing causal questions and elaborating the assumptions needed to answer them.[1-41] These frameworks have supported the refinement of existing methods and the

development of new methods that promise to deliver results that have a causal interpretation, provided strong assumptions are met.[42-138] Third, observational data from multiple sources (eg, registries, health care claims, electronic health records) are increasingly available for research purposes. Analyses from different sources can facilitate the evaluation of robustness by using data with different measurement characteristics from populations that may have different underlying causal structures.

In what follows, we first lay out the challenges inherent in drawing causal inferences about the effects of interventions from observational studies. We then discuss limitations of the current approach to determining the appropriateness of causal language for observational studies. Finally, we propose an alternative framework for causal inference in medical and health policy research and examine its implications for authors, reviewers, editors, and readers of clinical journals.

The Challenge in Drawing Causal Inferences From Observational Studies

Increasing use of observational studies to address questions about the causal effects of interventions poses a challenge to journals that primarily serve clinical audiences. These observational studies depend more heavily on causal and statistical modeling assumptions compared with large, well-conducted randomized trials. Therefore, all other study aspects being equal, drawing causal inferences from observational studies is inherently more speculative. But, as noted earlier, all other study aspects are often not equal. Randomized trials cannot address all causal questions of importance in medicine and health policy and may have limited generalizability; thus, investigators may need to use observational studies as a source of evidence to address causal questions. The challenge, then, is to balance the importance of addressing the causal questions for which observational studies are needed with caution regarding the reliance on strong assumptions to support causal conclusions.

When researchers are confronted with this challenge, one response is to retreat from causal goals and pursue purely descriptive or predictive goals for observational studies. This approach often amounts to applying a randomization-centered criterion for determining whether causal language is allowed, resulting in exclusively associational language for any investigation using observational data. With this approach, a single study design element essentially dictates the language that can be used to describe goals, methods, and interpretations. For example, current Instructions for Authors in *JAMA* and the JAMA Network journals state that "[c]ausal language (including use of terms such as effect and efficacy) should be used only for randomized clinical trials. For all other study designs..., methods and results should be described in terms of association or correlation and should avoid cause-and-effect wording." This recommendation is also included in the *AMA Manual of Style*.[139] Nevertheless, rare ad hoc exceptions have been made by *JAMA* and JAMA Network journals in allowing causal interpretations for observational analyses in which necessary assumptions were articulated and deemed plausible.[140,141] Furthermore, articles in the *JAMA* Guide to Statistics and Methods series have discussed various causal inference methods.[142-151]

Limitations of the Randomization-Centered Criterion for Determining the Appropriateness of Causal Language and Interpretation

The use of a binary, randomization-centered criterion for allowing the use of causal language or interpretation is not problematic when applied to large, well-conducted randomized trials with near-perfect adherence to the study protocol and limited missing outcomes, wherein a causal interpretation is warranted. However, for many other studies, the approach based on this criterion is inadequate and does not accommodate precise descriptions of goals, research questions, methods, assumptions, and interpretations, and can result in lack of clarity during interactions among authors, editors, reviewers, and readers. The prohibition impedes the presentation and critique of study methods and risks misinterpretation of results both by allowing inappropriately drawn implicit causal inferences and by obscuring appropriate causal conclusions.

Prohibiting causal language when describing observational studies does not allow authors to communicate their research goals clearly and fully.[152-154] Causal goals require causal assumptions (eg, the assumption of no uncontrolled confounding). These assumptions are almost never possible to verify with the data alone, and their plausibility can best be assessed within an explicit causal framework. Without causal language, the description and critique of research methods becomes challenging because the connection between ends (causal goals) and means (research methods) is obscured.[154] Furthermore, when causal goals, assumptions, and methods cannot be explicitly discussed, assessing the choice of study design and analytic approaches and interpreting results become difficult, if not impossible. In fact, avoidance of causal language precludes effective criticism grounded in causal considerations. For example, if a manuscript purports to present only descriptive or predictive associations between some exposure (or treatment) and outcomes, there is little room for discussing confounding in the sense of comparability between intervention groups.[153,154] Yet such discussion is often necessary to uncover the reported study's limitations if a causal interpretation is under consideration. In other words, restricting causal discourse is undesirable because authors and readers often hope that the estimated associations have a tenable causal interpretation and are interested to know when and why such interpretation may not be valid.

In addition, using a single study design element (randomization) as the sole criterion of whether causal conclusions can be drawn risks giving the impression of complacency about potential weaknesses that can affect both randomized trials and observational studies. Editors, reviewers, and readers would not draw causal conclusions based on simple between-treatment-group comparisons from a randomized trial with poor data collection practices, differential outcome ascertainment, or a high dropout rate, but these issues are not given the same weight as (lack of) randomization when the current approach to the use of causal language is applied. Arguably, an approach based on the randomization-centered criterion without directly confronting the difficulties listed earlier would be possible only if randomized trials with no major flaws were the only experimental studies under consideration, in which case cautions about causal interpretation

could be reserved only for observational studies. Randomization strengthens the plausibility of a causal interpretation of study results, but randomization alone is not sufficient. Conversely, the absence of randomization does not on its own render a causal interpretation completely untenable. For observational studies, the blanket prohibition of causal language skirts the difficult but necessary work of judging whether a causal interpretation of any specific observational analysis is tenable. This judgment cannot rest on simply noting the absence of randomization[155]; it requires context-informed examination of all relevant aspects of design, conduct, and analysis.

An Alternative Framework for Causal Inference for Medical and Health Policy Research

The extensive literature on causal inference across diverse disciplines[26,30,156-158] suggests an alternative framework for observational studies that aim to answer questions about the causal effects of interventions. This framework avoids the limitations discussed earlier and can help editors and readers determine whether a particular observational study provides valid and reliable evidence about the effects of interventions in a target population. Such a framework can be summarized in terms of several core questions that need to be considered to understand and interpret observational studies:

1. **What is the causal question?** If the goal of the research is to provide evidence about the effects of medical or health policy interventions, the research question is best explicitly framed in causal terms, comparing 2 or more well-defined alternatives with respect to clearly defined outcomes of interest, for a specific target population during a period of follow-up.[159,160]
2. **What quantity would, if known, answer the causal question?** After stating the causal question, one can specify the quantity that could, if known, serve as the answer to the question; this quantity is the *causal estimand* (eg, the causal effect of interest).[161,162] The precise specification of the causal estimand requires describing the population of interest, the interventions or strategies to be compared, details of outcome definitions and the timing of outcome ascertainment, and the choice of effect measure (eg, risk difference, relative risk). The causal estimand can be formally specified using mathematical causal models (eg, closely related counterfactual, potential outcome, or structural models[3,5,26,163-169]). In many cases, specification can be aided by describing the (hypothetical) target trial that could address the research question.[144,170-172]
3. **What is the study design?** The approach for collecting new data or using existing data—including choosing among data sources, sampling individuals and their follow-up experience, and collecting treatment covariate and outcome information over time—determines whether the data can be used to answer the causal question. For example, in cohort studies comparing different treatment strategies, the choice of the start of follow-up (time zero) and the alignment of that time with the time at which eligibility is determined can affect the validity of observational analyses.[173] More broadly, the key goal of study design is to make the causal assumptions more plausible and to facilitate learning about the causal estimand.
4. **What causal assumptions are being made?** Drawing causal inferences from observational studies requires causal assumptions that allow investigators to learn about the causal estimand by using data. For example, many observational studies require an assumption that, given the variables that have been measured and accounted for (via study design or analysis), there remains no uncontrolled confounding.[174] Other approaches, such as instrumental variable analyses, difference-in-differences analyses, or regression discontinuity analyses, require different sets of assumptions. Typically, causal assumptions are untestable in the sense that they cannot be fully evaluated with the data alone; instead, they have to be examined on the basis of background knowledge (eg, clinical knowledge of the treatment selection process).[175,176]
5. **How can the observed data be used to answer the causal question in principle and in practice?** Using the study design and causal assumptions, investigators can determine how analyses of observed data could, at least in principle (eg, if, hypothetically, all causal assumptions held and sampling variability were absent), provide information about the causal estimand. The formal examination of whether the observed data can in principle be used to learn about the causal estimand is referred to as *identification analysis*. In some cases, the assumptions suffice only to place bounds around the causal estimand.[45,177-179] Most studies aiming to estimate causal estimands using observational data rely on well-understood *identification strategies* (ie, the results from prior identification analyses)[180,181] and apply statistical methods to data for estimation and statistical inference. We offer a more detailed description of the relationship between causal estimands, identification analysis, and the use of data and statistical methods in the eText; eFigure 1, eFigure 2, and eFigure 3; and Example 1 and Example 2 in the Supplement.

   The statistical methods for observational studies should have good statistical performance (eg, acceptably low bias, high precision) and support the valid quantification of uncertainty (eg, producing valid CIs). The challenges of drawing statistical inferences using data and models are, if anything, accentuated in nonexperimental research.[182] Furthermore, issues related to missing data and measurement error often arise in observational studies and require additional assumptions (typically untestable using the data alone) about the structure of missingness or measurement error, additional data (eg, validation studies), and specialized methods to address these issues and properly quantify uncertainty.
6. **Is a causal interpretation of the analyses tenable?** Evaluating the appropriateness of endowing the results of an observational analysis with a causal interpretation typically requires untestable assumptions. Determining whether such interpretation is tenable, therefore, involves subjective judgments informed by background knowledge and an understanding of the research context, drawing on multiple sources of evidence. These judgments can be informed by triangulation of results across different analyses (eg, using different assumptions or other data sources)[183]; attempts to falsify the causal assumptions with the data, when possible (eg, negative control analyses[80,184]); and quantitative bias/sensitivity analyses and other methods to examine assumption violations.[19,185-191]

What This Framework Aims to Accomplish

This framework maintains the distinction between causation and association while addressing the limitations of approaches that rely on randomization as the sole criterion: it differentiates between causal ends and the statistical means to achieve them; supports the alignment between causal questions and the analyses used to answer them; increases transparency to facilitate scientific conversations; acknowledges that subjective judgments, informed by background clinical or policy knowledge, are unavoidable in observational studies; and aims to instill intellectual humility. Disagreements regarding the appropriate interpretation of observational studies among different stakeholders are always possible. This framework clarifies such disagreements by making the relevant considerations explicit and facilitates reasoning and debate.

Far from being a list of separate items, the framework highlights that multiple interrelated components are needed to report, evaluate, and interpret observational studies. For example, investigators will select study designs that are tailored to answer the causal question of interest and that support the plausibility of the causal assumptions needed to answer it. Similarly, study design and data analysis aspects can be arranged to facilitate the conduct of quantitative bias/sensitivity and falsification analyses, providing for the rigorous evaluation of assumptions. Background knowledge and understanding of the medical or policy context of the investigation is needed in all steps of the framework, from framing the research question to evaluating the plausibility of assumptions and evaluating whether a causal interpretation is tenable.

Interpreted practically, the framework allows the use of causal language to specify research questions and study goals (eg, in a manuscript's Introduction section); to describe study methods, assumptions under which the methods produce results that have a causal interpretation, and approaches for examining assumptions (eg, in the Methods section); and to reason about the plausibility of assumptions and the degree to which a causal interpretation is tenable in view of background knowledge while acknowledging the potential limitations of such an interpretation (eg, in the Discussion section). Two elements are central to this proposal for presenting observational studies: first, being explicit about the "if-then" (conditional) structure needed for their interpretation (eg, if certain assumptions hold, then a causal interpretation of the findings is tenable); and second, acknowledging that careful context-informed judgments are necessary to evaluate whether assumptions are plausible and a causal interpretation is tenable.

Last, although not the focus of this communication, the framework can also be applied to randomized trials and may be particularly helpful for pragmatic trials with baseline randomization that otherwise share many characteristics of observational studies (eg, trials with nonstandardized follow-up protocols and limited systematic efforts to enhance adherence to the assigned treatment).[192,193]

What the Framework Does Not Do

The framework does not imply that all, or even most, observational studies merit a causal interpretation. For some observational studies that start with causal goals, causal inference may prove impossible; in these cases, estimates retain only associational interpretations. In addition, many important descriptive and predictive research questions can be answered by observational studies that do not require causal notions.

Furthermore, when addressing causal questions, our proposal does not single out any of the currently popular frameworks, empirical research strategies, or statistical methods for causal inference from observational studies (eg, structural approaches[27,167]; identification strategies[180,181]; the target trial framework[144,170]; the causal roadmap and targeted learning[32,156]; any specific statistical, epidemiologic, or econometric method), nor does it single out any philosophy of statistical inference (eg, frequentist, bayesian). There is room for creativity in approaching practical causal questions, and investigators should have the freedom to select the approaches that best suit their research questions, provided they follow the norms for reporting described earlier. Without delving into the details of a specific research question, perhaps the most that can be recommended is to use the simplest methods that are adequate for the study's causal goals.[194,195]

The framework does not address the broader issue of how to determine whether some general causal claim is warranted (eg, whether some exposure is a "cause" of some outcome). Instead, it focuses on whether observational studies can contribute independent credible evidence about causal effects of interventions in a particular target population, time, and place. Reports of such studies are the core publication type in most medical and health policy journals; more important, they are a key input to the process of evidence synthesis that can support general causal claims. This process combines information from multiple sources, including—in addition to trials and observational studies comparing interventions—basic science investigations, case reports, noncomparative studies, meta-analyses, and simulation modeling studies, as well as background knowledge.

Last, the framework does not cover other important issues that apply broadly to empirical investigations regardless of study design, such as prespecifying and preregistering analyses, following the principles of reproducible science, and sharing research materials.

Implications for Authors, Reviewers, Editors, and Readers

Adoption and further elaboration of the framework outlined earlier by medical journals offer the promise of facilitating communication between authors, reviewers, editors, and readers, but come with challenges in operationalization and implementation.

For authors, the framework provides more freedom to express causal goals and assumptions of observational studies, but also entails the responsibility to explicitly discuss and evaluate assumptions and openly acknowledge limitations (eg, violations of assumptions) and may require additional work (eg, to report technical details; to conduct triangulation, falsification, and bias analyses).

For reviewers, the framework should aid in the assessment of manuscripts that report observational studies. It requires familiarity with causal inference methods, as well as background knowledge to judge the appropriateness of the methods in the context of applied work.

Adoption of the framework should facilitate communication between authors, reviewers, and editors by encouraging the

transparent reporting and critique of methods and results of observational studies of medical interventions. Implementation at scale will require retaining expert reviewers and increasing the cooperation between editors, authors, and reviewers to operationalize the framework for use with different analyses and specific clinical applications and to evaluate whether it improves the reporting of empirical research. Furthermore, the complex judgments that the framework entails require vigilance to mitigate cognitive biases and distortions that may influence the presentation and interpretation of observational studies, particularly those using technically complex methods.[196]

For readers, the framework should facilitate the clear communication of causal questions and methods. As usual, detailed technical descriptions may be appropriately placed in supplemental appendices to allow for the inclusion of the necessary detail and to maintain the readability and accessibility of the published study. Although our proposal suggests that complex concepts and more elaborate methodological descriptions may be needed to fully report and evaluate observational studies, adoption of the framework promises to improve the value of applied research that can support medical and policy decisions.

We look forward to readers' reactions to the framework. In future communications, we plan to explore its application in the context of concrete examples of specific types of observational analyses typically encountered in medical journals such as *JAMA* and the JAMA Network journals.

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